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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,449	11/09/2005	Isabelle Poquet	1169-034	3827

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EXAMINER	
MARVICH, MARIA	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
12/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,449	POQUET ET AL.	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-35* is/are pending in the application.

4a) Of the above claim(s) *22-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-21 and 31-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 8/6/09. Claims 12-35 are pending in this application. Claims 22-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b). Therefore, claims 12-21 and 30-35 are under examination.

Applicants have incorrectly noted that withdrawn claims are "presently presented". In the interest of compact prosecution the amendment was accepted. However, applicants should note that withdrawn claims should be accompanied by the status identifier "withdrawn".

Specification

The amendments to the specification to correct the priority statement as well as the objections to the formatting.

Claim Objections

Claim 13, 14 and 35 are objected to because of the following informalities: claim 13 recites that the P_{zn} promoter comprises SEQ ID NO:2. However, more accurately, it is the ZitR binding site that comprises SEQ ID NO:2. It would be remedial to recite, --wherein the ZitR binding site comprises the following sequence--. Similar amendment to claim 14 is recommended.

It is recommended that claim 19 and 20 be amended to recite more directly, --the expression cassette of claim 12--. It is noted that "Claim" should be written in lower case in the dependent claims.

Claim 35 recites that the sequence encoding the polypeptide of b) has at lest 85% identity with GenBank AAK06214. It is proper to recite that the sequence is --deposited under accession number AAK06214--.

Appropriate correction is required.

Claim 15 was previously objected to for being a substantial duplicate of claim 12. Claim 12 is drawn to an expression cassette comprising pZn and a sequence encoding a ZitR polypeptide and further comprising a restriction site for insertion of sequences. Claim 15 is drawn to an expression cassette comprising pZN from claim 12 and a restriction site. Applicants have argued that claim 15 is intended on reading on only the promoter of claim 12 and to exclude the remaining recited limitations of claim 12 i.e. sequences encoding ZitR. Such a claim construction is improper. A dependent claim must incorporate all of the limitations of the claim from which it depends. Hence, claim 15 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. See MPEP 608.(i), "Claims in dependent form shall be construed to include all the limitations of the claim incorporated by reference into the dependent claim."

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-21 and 31-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an expression cassette comprising SEQ ID NO:1 operably linked a sequence encoding a polypeptide with at least 85% identity with the *Lactococcus lactis* ZitR protein encoded by nucleotides 357-794 of SEQ ID NO:9 wherein the polypeptide is obtained from Lactococcus further operably linked to a restriction site, does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. **This rejection is newly worded based upon applicants' amendment.**

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples~ state of the art, predictability of the art, the amount of experimentation necessary and the relative skill levels of those in the art. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The instant claims are drawn to a cassette designed for zinc-regulated expression of genes in gram-positive bacteria. The invention is based upon the observation that the ZitR repressor can bind and form a complex with affinity for the -35 box of SEQ ID NO:1 to repress transcription. In the absence of zinc, transcription ensues. Hence, applicants propose use of promoter elements comprising SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:4 and SEQ ID NO:5 which share the common feature of the -35 box of the *Lactococcus lactis* operon promoter which also serves as the binding site for ZitR.

The constructs of the instant invention also include 1) insertion sites for nucleotides of interest to be expressed under control of pzn 2) excludes inclusion of ZitS and a reporter gene 3) inclusion if a signal peptide to create fusion peptides comprising the signal peptide.

Case law has established that ' (t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.'" In re Wright 990 F.2d 1557, 1561. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that ' (t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". In this case, applicants disclose that the coding sequence of ZitR is found in figure 2 or as SEQ ID NO:9.

A review of this art demonstrates that the ability to *de novo* protein model is not routine but requires vast computation even a single mutation can greatly effect even simple structural formations of the resultant protein.. A particular protein sequence determines the protein's structural, and functional properties, and a predictability of a representative number of claimed polypeptide sequences that display noteworthy biological properties requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which a protein's structure relates to its functional usefulness(see Guo et al and Lesk et al). Hence, the ability to determine a priori whether a homologue or variant can function in the recited invention is not a high art. A particular protein sequence determines the protein's structural, and functional properties, and a predictability of a representative number of claimed polypeptide sequences that display noteworthy biological properties requires a

knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which a protein's structure relates to its functional usefulness. One of skill in the art would recognize that analyzing all permutation s of sequences comprising any combination of minimally 38 mutations to maximally 100 nucleotides would require undue experimentation despite the demonstration of protocols to do so.

In view of the unpredictability of the art of predicting the functional and structural nature of related sequences of undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the unpredictability of the art, the poorly developed state of the art with regard to predicting the structural/ functional characteristics of a protein from primary sequence alone, the lack of adequate working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue, unpredictable experimentation to practice the claimed invention.

Response to Amendment

Applicants amendments filed 8/6/09 have been persuasive in overcoming the rejection under 35 USC 112, first paragraph in part. However, based upon applicants' amendment the rejection newly presented is based upon the lack of limiting identification of the Lactococcus lactis ZitR protein coding sequences. The specification teaches that the Lactococcus lactis protein is encoded by SEQ ID NO:9. There is but one sequence for this protein . As well, the breadth of proteins encompassed by at least 80% in relationship to what is known in the art and

the specification encompasses a number of inoperable embodiments. By applicants own admission there are no proteins from Lactococcus that are less than 88% identical to SEQ IDNO:9. "Lactis 111403 (GenBank AAK06214) are ZitR proteins, namely the ZitR protein of L. lactis subsp, cremoris MG1363 (88% identity) and the ZitR protein of L. lactis subsp, cremoris SK11 (89% identity). As a matter of fact there is no protein having at least 80% identity with GenBank AAK06214 which is not a ZitR protein. The next proteins which have the higher homology with ZitR are Streptococcus proteins which have at most 54% identity with GenBank AAK06214. Therefore, it is very unlikely that one can isolate a protein having 80% identity or more with GenBank AAK06214 which is not a ZitR protein".

It is noted that insertion of the reference sequence will overcome the rejection to claims 31-34.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 35 is rejected under 35 U.S.C. 112, first paragraph, because claim 35 refers to biological deposits to satisfy the "how to make" requirement, but fails to specify the details of the sequence such that one of skill in the art can produce the recited cells. **This is a new rejection necessitated by applicants' amendment.**

More particularly, claim 35 is drawn to or encompasses use of a specific sequence deposited under Genbank accession number AAK06214. As such, this application discloses a

sequence that is encompassed by the definitions for biological material set forth in37 C.F.R. 1.801. Because it is apparent that this biological material is essential for practicing the claimed invention, it must be obtainable by a reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. 1.801 through 1.809.

It is unclear that the sequence of claim 35 will be readily available to the public or that the written instructions are sufficient to reproducibly construct this biological material from starting materials known and readily available to the public. Therefore, in order for a deposit to meet all criteria set forth in 37 C.F.R. 1.801 through 1.809, Applicant or Assignee must provide assurance of compliance with provisions of 37 C.F.R. 1.801-1.809 in the form of a declaration or Applicant's representative must provide a statement. The content of such a declaration or statement is suggested by the encoded attachment. Because such deposit will not have been made prior to the effective filing date of the instant application, Applicant is required to submit a verified statement from a person in a position to corroborate the statement that the biological material which had been deposited is the biological material specifically identified in the applicants as filed (37 C.F.R. 1.804). Such a statement need not be verified if the person is an agent or attorney registered to practice before the Office. Applicant is also reminded that the specification must contain reference to the deposit, including deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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